A Method for Statistical Process Control of Radiation Sterilization Facilities

Revision 1, 2018

PANEL ON GAMMA & ELECTRON IRRADIATION

A Method for Statistical Process Control (SPC) of Radiation Sterilization Facilities

Foreword to the 2018 revision

In 2017, a revised version of the EN/ISO standard 11137-3 “Sterilization of health care products - Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control” was published. The 11137-3:2017 standard references this Irradiation Panel SPC document as published in 2006. Both documents are consistent in terms of technical concepts, but the terminology used is different and this represents a potential source of confusion. In particular, the 2006 Panel SPC document defines a “target dose” in terms of dose at the minimum dose location within an irradiation container, whereas 11137-3:2017 uses the same term to refer to a dose at the routine monitoring position. This 2018 revision has been prepared with the aim of harmonizing the terminology with that used in 11137-3:2017. Apart from the change in the position at which the target dose has been defined, no other technical changes have been made and the 2006 and 2018 versions of this document can be considered to be equivalent. It is intended that this document will be reviewed again for relevance and consistency with industry standards after the publication of ISO TS 11137-4 “Sterilization of health care products – Radiation – Part 4: Guidance on the establishment and control of the irradiation process”, which is currently under development and builds on to the concept of establishing target dose(s) as introduced in EN ISO 11137-3:2017.

Scope

This document describes a Statistical Process Control Method for the operation of industrial radiation sterilization facilities. It presents an alternative to current methods of operation by utilizing knowledge of process characteristics and measurement uncertainties in the establishment and routine monitoring of the process.

Introduction

Control of the radiation sterilization process has historically been based on analysis of individual dose measurements to ensure they are within defined upper and lower limits. These limits are set based on the required *sterilization dose* and the *maximum acceptable dose* and may also include allowance for various process uncertainties, such as dosimetry uncertainty and dose mapping uncertainty. Allowance for uncertainty is either based on quantitative information or estimated “safety factors”. This historical approach takes no account of the statistical nature of many aspects of the process and can result in unnecessary investigation or product rejection when dose readings fall outside defined limits. An apparently “out of specification” reading may, in fact, be consistent with a process running in control when account is taken of the known random variation associated with the process. Rather than pass / fail decisions being taken on each individual dose measurement, the observed range in a sequence of dose measurements can be compared with the expected range based on the known characteristics of the process. Decisions can then be made based on statistical justification that the dose received by product is within specification.

The Method of Statistical Process Control described in this document takes account of dosimetry and

process uncertainties to derive a target dose for each type of product and removes the need to build in estimated “safety factors”. Once a target dose has been established, the process can be monitored with dosimeters to ensure that deviations from this dose are within the range that would be expected from prior knowledge of plant and dosimeter performance. The Method assumes that the process can be set up in such a way that the dose to product can be predicted and the observed variation from this prediction will be due to quantifiable random effects. This is generally the case for electron beam irradiators that treat a single container at a time, but will be more difficult to achieve with gamma irradiators in which the dose is dependent not only on plant parameters, but also on the nature of other product within the irradiator. Options are given in this Method to take account of this problem.

The Method builds on the concepts outlined in a previous document entitled “Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB Plants”, published by the Irradiation Panel (see Annex A). The “Discussion Paper” describes the various components of uncertainty that affect delivery and measurement of dose in the radiation sterilization process and presents methods for establishing the magnitude of these components. It is recommended that readers familiarize themselves with the concepts in the “Discussion Paper” before attempting to follow this Method.

Defined terms used in this Method are consistent with those in EN ISO 11137-1:2015 and EN ISO 11137-3:2017. For completeness, a Glossary of relevant terms is given in Annex B and these are also shown in italics in this document.

Overview

The SPC method described below uses a probability based approach to determine the appropriate *target dose* for running the sterilization process (D_{target}). The *target dose* is defined as the dose required to be delivered at the routine dose monitoring position. This approach takes into account the total standard uncertainty associated with the delivery and measurement of the minimum and maximum dose in an irradiation container. These uncertainties are determined during the calibration of the dosimetry system, during *Operational Qualification*, and during *Performance Qualification*.

The method uses standardised control charts to record the doses measured during routine processing. This allows data from multiple products to be recorded on a single chart and control limits to be predefined. The points plotted represent standardised values of the form $(x - \mu) / \sigma$, where x is the dose measured, μ is the *target dose* and σ is a measure at 1 standard deviation of the expected variability in the dose. The process is considered to be in control if the doses measured are within the range of doses that would be expected based on the statistical variability of both the irradiation process and the dose measurement.

The following steps describe the SPC method:

Step 1: Calculation of total process uncertainty

For each product, calculate the total standard uncertainty ($\sigma_{process}$) associated with the delivery and measurement of the minimum and maximum dose in an irradiation container. These should be expressed as percentages at 1 standard deviation and are designated $\sigma_{process}^{min}$ and $\sigma_{process}^{max}$, respectively. Descriptions of these various components of uncertainty and typical methods for estimating their values are given in Annex A.

Two cases need to be considered:

i) **In the case of irradiators in which the dose to product can be predicted purely on the basis of machine settings**, for example most electron beam irradiators and certain specialised gamma irradiators, the relevant total uncertainty will consist of the following components of uncertainty

combined in quadrature:

a) dosimeter calibration uncertainty, σ_{cal}
b) dose mapping uncertainty, σ_{map}
c) dosimeter reproducibility, σ_{rep}
d) machine variability, σ_{mach}.

$$\sigma_{process} = (\sigma_{cal}^2 + \sigma_{map}^2 + \sigma_{rep}^2 + \sigma_{mach}^2)^{½} \qquad \text{Eqn. 1}$$

ii) **In the case of irradiators in which the dose to product is influenced not only by machine settings, but also by the variability of other product within the irradiator**, for example the majority of gamma irradiators, the relevant total uncertainty will consist of components a), b) and c) above. As the dose received by product will also depend, to some extent, on other product within the irradiator, it is generally not possible to predict a value of $\sigma_{mach.}$ This means that conventional statistical process control techniques are not applicable. However, the standardised control charts described in this Method can be used to monitor irradiator performance and provide information on the effectiveness and efficiency of the process.

Step 2: Specification of level of confidence

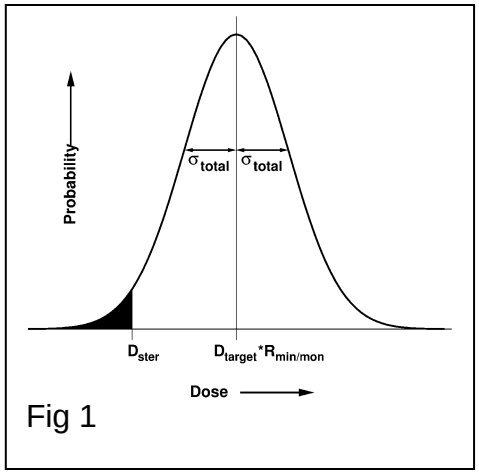

Fig 1

It is necessary to specify the level of confidence (*p*) required for the process, where *p* represents the probability of product in an irradiation container receiving less than the *sterilization dose*. This is shown schematically in Fig 1 where the bell shaped curve represents the probability of product at the position of minimum dose in an irradiation container receiving a given dose when processed at a *target dose* of D_{target}. The factor $R_{min/mon}$ is the ratio of dose at the minimum dose position in an irradiation container to the dose at the routine monitoring position and is determined during dose mapping. This is needed as D_{target} is defined in terms of dose at the routine monitoring position. The *target dose* is chosen to ensure that the proportional area of the curve below D_{ster} is less than the specified level of confidence. This can be expressed mathematically to define a lower target dose value as:

$$D_{target}^{lower} = D_{ster} / (1 - k * \sigma_{process}^{min} / 100) / R_{min/mon} \qquad \text{Eqn. 2}$$

where D_{ster} is the *sterilization dose* and $\sigma_{process}^{min}$ is the total standard uncertainty associated with the

delivery and measurement of dose at the minimum dose position in an irradiation container. The value of "*k*" is dependent on the specified level of confidence and is equal to 2.326 for p= 0.01 i.e. at a 99% level of confidence that the dose at the minimum dose location exceeds the *sterilization dose*. The equivalent value of *k* is 1.645 for p= 0.05. In practice, a value of *k*=2 may be an appropriate choice, corresponding to a level of confidence of approximately 98% i.e. the black shaded area in Fig 1 is approximately 2% of the total area under the curve. A more detailed derivation of Eqn. 2 is given in Annex D.

An analogous expression applies in respect of the *maximum acceptable dose* where an upper target dose value can be expressed as:

$$D_{target}^{upper} = D_{max,acc} / (1 + k * \sigma_{process}^{max} / 100) / R_{max/mon} \qquad \text{Eqn. 3}$$

where $D_{max,acc}$ is the *maximum acceptable dose* and $\sigma_{process}^{max}$ is the total standard uncertainty associated with the delivery and measurement of dose at the maximum dose position in an irradiation container.

Step 3: Selection of target dose (D_{target})

For each product, the *sterilization dose*, the *maximum acceptable dose* and the process uncertainties at the minimum and maximum dose positions are used to determine D_{target}^{lower} and D_{target}^{upper} that represent the acceptable operating window for the mean of the process D_{target}. A value of D_{target} within this window is then selected for use in routine processing.

As an example, consider the following (taken from Annex C):

k = 2 (corresponding to level of confidence of approximately 98%)	
Sterilization dose D_{ster}:	16.1 kGy
Maximum acceptable dose $D_{max,acc}$:	35 kGy
$\sigma_{process}^{min}$:	5.6%
$\sigma_{process}^{max}$:	5.9%
$R_{min/mon}$	0.88
$R_{max/mon}$	1.38

Using Eqn. 2, a lower limit for the target dose of 16.1/(1-2*5.6/100) / 0.88 = 20.6 kGy is obtained, based on the requirement to deliver a dose greater than the *sterilization dose*.

Similarly, using Eqn. 3, an upper limit for the target dose of 35/(1+2*5.9/100) / 1.38 = 22.7 kGy is obtained, based on the requirement not to exceed the *maximum acceptable dose*.

To summarise, if D_{target} is set within the operating window 20.6 kGy to 22.7 kGy then a process having at least a 98% probability that product has received greater the *sterilization dose* and less than the *maximum acceptable dose* can be achieved. The actual choice of D_{target} will be influenced by local operational considerations.

Step 4: Calculation of charting data

Having selected an appropriate value of D_{target} for each product, it is now possible to monitor the process using dosimetry. If the process is under statistical control, the measured doses at the monitoring position will be centred around D_{target} and will exhibit a spread consistent with the variability expected from the various components of uncertainty derived in Step 1. The observed variability will, in general, arise from the random statistical behaviour of the dosimetry system and the irradiator. Uncertainty due to dose mapping is taken into account in setting D_{target}, but will not contribute to the

observed variability of the process. Similarly, dosimeter calibration uncertainty will also not contribute to observed "day-to-day" variability, but may be apparent as a step change in control charts when a newly calibrated set of dosimeters is used. Such changes may require a re-evaluation of D_{target}. This is discussed in more detail in the document "Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB Plants", see Annex A.

Plot points, P_{plot}, can now be calculated according to the formula:

$$P_{plot} = (D_{meas} - D_{target}) / \sigma_{plot} \qquad \text{Eqn. 4}$$

where D_{meas} is the measured dose at the monitoring position and σ_{plot} is the expected variability associated with the monitoring dose measurements for the product concerned.

In determining σ_{plot}, two cases need to be considered:

i) **In the case of irradiators in which the dose to product can be predicted purely on the basis of machine settings**, for example most electron beam irradiators and certain specialised gamma irradiators, the expected observed variability, σ_{plot}, will consist of the uncertainty due to dosimeter reproducibility and machine variability, combined in quadrature:

$$\sigma_{plot} = D_{target} / 100 * (\sigma_{rep}^2 + \sigma_{mach}^2)^{½} \qquad \text{Eqn. 5}$$

Note: In order to simplify the calculation of individual plot points, σ_{plot} is expressed in terms of dose, whereas σ_{rep} and σ_{mach} are expressed as percentages.

ii) **In the case of irradiators in which the dose to product is influenced not only by machine settings, but also by the variability of other product within the irradiator**, for example the majority of gamma irradiators, the only predictable statistical source of variability is the uncertainty due to dosimeter reproducibility, i.e.

$$\sigma_{plot} = D_{target} / 100 * \sigma_{rep} \qquad \text{Eqn. 6}$$

Note: In order to simplify the calculation of individual plot points, σ_{plot} is expressed in terms of dose, whereas σ_{rep} is expressed as a percentage.

Additional variability in observed measurements will arise from variations in irradiator conditions such as variations in other product present in the irradiator. As these are not predictable statistical variations, they cannot be used in statistical process control. However, the chart plotted in Step 5 can be used to indicate when dose measurements are outside the range that could be attributed to statistical dosimeter variability.

Step 5: Charting and interpretation of data

Sequential values of P_{plot} are plotted onto a chart, with appropriate warning and action limits. It is suggested that warning limits are set at ±2.5 and action limits at ±3.5 i.e. at deviations of $\pm 2.5\sigma_{plot}$ and $\pm 3.5\sigma_{plot}$, respectively. The choice of limits represents a balance between an excessive number of false alarms and the possibility of missing genuine "out of specification" readings.

A process running in statistical control will exhibit a distribution of plot points centred around zero.

Plot points between the 2.5 and 3.5 limits should be investigated and possible *preventive action* taken.

Plot points outside the 3.5 limits require immediate investigation and *corrective action*. This may involve re-establishment of the process parameters.

Note: Although a plot point above the +3.5 standard deviation limit is not of concern with respect to the achievement of the *sterilization dose*, it must be reviewed to determine if the *maximum acceptable dose* has been exceeded.

The control chart should also be monitored for trends that may indicate the process is drifting out of control. This enables *preventive actions* to be taken in advance of the action limit being reached.

An increase in the magnitude of short-term fluctuations in the chart may be indicative of problems with the dosimetry system or, in the case of electron beam irradiators, the machine control system.

The chart limits are based on an estimate of the expected behaviour of the process. They should be reviewed periodically against the actual spread of dose measurements and adjustments made as necessary.

Bibliography

1. "Guidelines for the Calibration of Dosimeters for use in Radiation Processing", Peter Sharpe and Arne Miller, NPL Report CIRM 29, NPL, Teddington TW11 0LW, UK, (2009) http://www.chemdos.npl.co.uk/docs/NPLReportCIRM29.pdf

2. "Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB Plants https://www.irradiationpanel.org/app/download/3781373/Guide+Uncertainty+in+Routine+Dosimetry+1998.pdf, (1998)

3. "EN ISO 11137-1:2015 Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices", International Organization for Standardization, Case Postale 56, CH-1211, Geneva, Switzerland.

4. "EN ISO 11137-3:2017 Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects", International Organization for Standardization, Case Postale 56, CH-1211, Geneva, Switzerland.

Annex A - Methods for Calculation of Components of Uncertainty

Suggested methods for calculating various components of uncertainty are given in the document "Guidelines for the Calibration of Dosimeters for use in Radiation Processing", Peter Sharpe and Arne Miller, NPL Report CIRM 29, (2009), available at http://www.chemdos.npl.co.uk/docs/NPLReportCIRM29.pdf

For a more general discussion see "Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB Plants" available at https://www.irradiationpanel.org/app/download/3781373/Guide+Uncertainty+in+Routine+Dosimetry+1998.pdf

Dosimeter Calibration Uncertainty (σ_{cal})

The uncertainty due to dosimeter calibration is a combination of the uncertainty in measurements, or irradiations, carried out by the calibrating laboratory, the uncertainty in fitting the derived calibration function and, in some situations, uncertainties arising from environmental influence effects. In situations where a different dosimetry system is used for dose mapping and routine monitoring, it is necessary to include the calibration uncertainty of both systems. See CIRM 29 for further details.

Dose Mapping Uncertainty (σ_{map})

The uncertainty due to dose mapping can be derived from replicate dose maps made during *Performance Qualification*. At least 3 replicate dose mapping exercises should be carried out, but confidence would be increased by undertaking a greater number. The usual approach is to calculate the minimum/monitor and maximum/monitor dose ratios for each of a number of dose maps and then determine the mean minimum/monitor and maximum/monitor ratios and the sample standard deviations of the respective dose map ratios, expressed as percentages of the means. An example of this calculation is given in Annex C.

Dosimeter Reproducibility (σ_{rep})

The relevant uncertainty is the reproducibility of the dosimetry system that is used to routinely monitor the process. The uncertainty due to dosimeter reproducibility can be determined from the standard deviation observed between the readings of a number of dosimeters irradiated to the same dose. This is usually most conveniently determined during dosimeter calibration. See CIRM 29 for further details.

Note: If multiple dosimeters are used to make each dose measurement during routine processing, e.g. a number of dye films within a single package, the relevant Dosimeter Reproducibility is that associated with the mean of the readings. For example, if the reproducibility of the individual dosimeters has been determined to be 2% and 3 dosimeters are used to make each dose measurement, then the reproducibility associated with the measurement is $2/\sqrt{3}$ %.

Machine Variability (σ_{mach})

The uncertainty due to machine variability can be determined from the scatter between monitor dose measurements made at different times using identical machine settings. The observed variability may be influenced by tolerances in machine parameter settings and feedback systems. Determination of this variability forms part of *Operational Qualification*.

It is often difficult to separate Machine Variability and Dosimeter Reproducibility and the uncertainty determined will often be a combination of the two. For example, the scatter between calorimeter measurements made on an electron beam machine with identical settings but at different times and with different calorimeters will comprise both machine variability and calorimeter reproducibility ($\sigma_{rep}^2 + \sigma_{mach}^2)^{½}$. Fortunately, these two components are used in combination in Step 4, Case i) and so the measured value can be used directly to derive σ_{plot}.

Annex B – Glossary of Terms

maximum acceptable dose
dose given in the process specification as the highest dose that can be applied to a defined product without compromising safety, quality or performance [EN ISO 11137-1:2015]

standard measurement uncertainty
measurement uncertainty expressed as a standard deviation [JCGM 200:2012]

statistical process control
application of statistical methods to identify and control the special cause of variation in a process.

sterilization dose
minimum dose to achieve the specified requirements for sterility [EN ISO 11137-1:2015]

uncertainty
non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used [JCGM 200:2012]

Symbols [EN ISO 11137-3:2017]

Symbol	Meaning
$D_{max,acc}$	maximum acceptable dose determined in accordance with EN ISO 11137-1:2015 , 8.1
D_{ster}	sterilization dose determined in accordance with EN ISO 11137-1:2015 , 8.2
D_{max}	direct measurement of maximum dose in a given irradiation container
D_{min}	direct measurement of minimum dose in a given irradiation container
D_{mon}	direct measurement of dose at the routine monitoring position
$R_{max/mon}$	ratio of maximum to monitor dose (determined by dose mapping D_{max}/D_{mon})
$R_{min/mon}$	ratio of minimum to monitor dose (determined by dose mapping D_{min}/D_{mon})
D_{target}^{lower}	calculated dose at the routine monitoring position used for establishing process parameters that ensures at a specified level of confidence that D_{ster} is met or exceeded during routine processing
D_{target}^{upper}	calculated dose at the routine monitoring position used for establishing process parameters that ensures at a specified level of confidence that $D_{max,acc}$ is not exceeded during routine processing

Annex C – Worked example

This Annex contains a worked example involving an electron beam irradiator.

Consider an electron beam irradiator using dye film dosimeters for dose mapping and calorimeters for routine monitoring. The required *sterilization dose* is 16.1 kGy and the *maximum acceptable dose* is 35 kGy. All uncertainties are expressed at 1 standard deviation.

Calibration uncertainty

Both dye films and calorimeters were calibrated using reference dosimeters from a calibration laboratory. As the same type of reference dosimeters were used for the calibration of both systems, the uncertainty from the calibration laboratory (1.5%) only needs to be included once. The statistical uncertainty in deriving the calibration function for the calorimeters was 1% and for the dye films was 2%. The overall calibration uncertainty (σ_{cal}) is, therefore, $(1.5^2 + 1^2 + 2^2)^{½} = 2.7\%$

Dose mapping uncertainty

Three replicate dose maps were carried out:

Dose map	D(minimum) D_{min}	D(maximum) D_{max}	D(monitor) D_{mon}	D_{min} / D_{mon}	D_{max} / D_{mon}
1	21.57	35.63	25.17	0.86	1.42
2	22.68	34.86	24.48	0.93	1.42
3	22.25	33.53	25.6	0.87	1.31
Mean	22.17	34.67		0.88	1.38
St. dev.				0.04	0.06
%				4.2	4.6

The dose mapping uncertainty at the minimum dose location D_{map}^{min} is therefore 4.2% and the dose mapping uncertainty at the maximum dose location D_{map}^{max} is 4.6%.

Dosimeter Reproducibility and Machine Variability

A combined value for the dosimeter reproducibility and the machine variability has been obtained previously from the observed scatter in multiple calorimeter readings irradiated with the same machine settings. This combined variability, $(\sigma_{rep}^2 + \sigma_{mach}^2)^{½}$, is equal to 2.5%.

Calculation of total process uncertainty

Using equation 1 and the above data, the following process uncertainties can be calculated for the minimum and maximum dose positions in an irradiation container:

$\sigma_{process}^{min} = (2.7^2 + 4.2^2 + 2.5^2)^{½} = 5.6\%$

$\sigma_{process}^{max} = (2.7^2 + 4.6^2 + 2.5^2)^{½} = 5.9\%$

Selection of target dose

Using equation 2 and a value of *k*=2, the value for D_{target}^{lower} necessary to achieve a dose in excess of the *sterilization dose* is:

$D_{target}^{lower} = 16.1 / (1 – 2*5.6/100) / 0.88 = 20.6$ kGy

Similarly, using equation 3 the value of D_{target}^{upper} necessary not to exceed the *maximum acceptable dose* is:

$D_{target}^{upper} = 35 / (1+ 2*5.9/100) / 1.38 = 22.7$ kGy

Based on the above calculations, a target dose between 20.6 kGy and 22.7 kGy could be used, the actual value chosen being influenced by local operational considerations. In this example, a D_{target} of 21.6 kGy was selected.

Calculation of charting data

The relevant plotting uncertainty σ_{plot} is given in equation 5 and is equal to:

$\sigma_{plot} = D_{target} / 100 * (\sigma_{rep}^2 + \sigma_{mach}^2)^{½} = 21.6 / 100 * 2.5 = 0.54$ kGy

The points to be plotted for this product are therefore calculated using the formula (Eqn. 4):

$P_{plot} = (D_{meas} – 21.6) / 0.54$

Where D_{meas} is the dose measured by the monitoring calorimeter.

Example of chart

An example of a control chart is given in Fig. 2 below. The readings are centred around zero, but with occasional values outside the warning and action limits. Longer term trends are also visible, indicating drift in some of the process parameters.

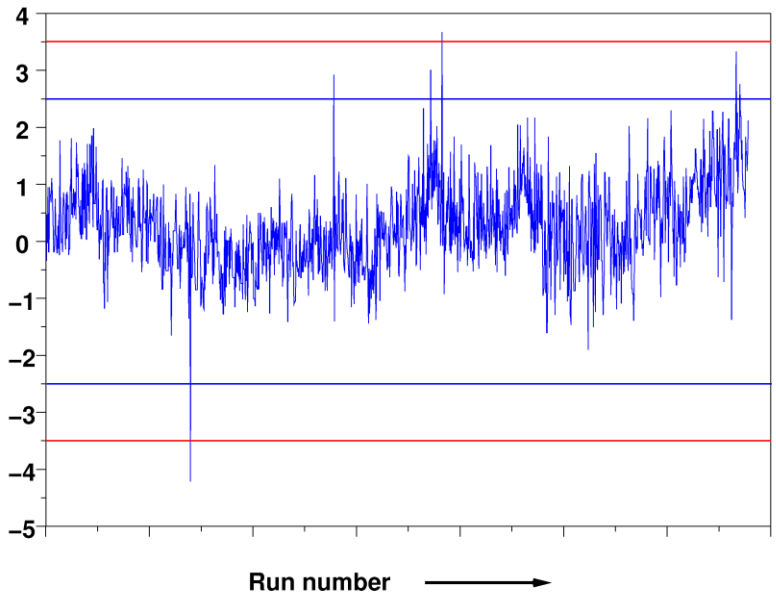

Fig 2 Example of a control chart

Annex D – Methodology for calculating D_{target}

A process following the Normal distribution has a mean μ and standard deviation σ.

If *x* is defined as the *sterilization dose* then the probability of receiving a dose less than this is determined as …

$$Prob[Dose < x] = P\left[Z < \frac{x-\mu}{\sigma}\right]$$

Suppose we are dealing with a Two Nines process (0.99), then

$$Prob[Dose < x] = 0.01$$

This is represented by…

$$P\left[Z < \frac{x-\mu}{\sigma}\right] = P[Z < -2.326]$$

This constant value is determined from the Standardised Normal Tables.

$$\frac{x-\mu}{\sigma} = -2.326$$

$$\mu = x + 2.326\ \sigma$$

The variation σ is more commonly represented as the percentage σ_p, where $\sigma = \frac{\sigma_p \mu}{100}$

$$\mu = x + 2.326\frac{\sigma_p \mu}{100}$$

$$\mu\left[1 - 2.326\frac{\sigma_p}{100}\right] = x$$

$$\mu = \frac{x}{\left[1 - 2.326\frac{\sigma_p}{100}\right]}^{*}$$

*A constant "*k*" of –2.326 is suitable for a Two Nines Process (99%). A process where 95% of the measured doses are greater than the *sterilisation dose* involves a constant of –1.645. In practice, a value of *k* = 2 is often chosen, corresponding to level of confidence of approximately 98%.